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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,432	10/15/2001	Chen-Kun James Shen	08919-016003	3256

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,432	SHEN, CHEN-KUN JAMES	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/27/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 05/27/04 has been acknowledged.
Claims 33-63 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/27/04 has been entered.

Claim Rejections - 35 USC § 103

Claims 33-36, 41-46, 51-53 and 58-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record*) in

view of Miller et al (Biotechniques 7(9):980-990, 1989 *ref of record),* for the same reasons of record as set forth in the office action mailed on 05/03/04.

The instant claims are drawn to an expression vector comprising a transcriptional start site; a promoter operably linked to the transcriptional start site; and a ζ-globin enhancer (SEQ ID NO:1) operably linked to the promoter, wherein the expression vector is a viral vector.

Zhang teaches an expression vector comprising, a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). The cited art teaches a HS-40 enhancer element (NF-E2/AP1-II) which comprises the nucleotide sequence of SEQ ID NO:1 (**tctgagtca,** ζ-globin enhancer as claimed) see page 8503, fig-1B, 3'NF-E2/AP1-II. The cited art further teaches nucleotide sequcnes of comprsing SEQ ID NO:1, 2 and 3 (see page 2299, fig-1B) in additon to introduction a a point mutation which comprsies changing gctgagtca to **t**ctgagtca to enhance the transcription of a gene of interest (page 2302 fig- 7). The cited art further teaches a method of expressing p-HS40 (3'NF-E2/AP1-II)-ζ597GH expression vector into isolated K562 erythroid cells. The K562 cells were transfected with expression vector and the expression of growth hormone was measured by GH assay and/or RNA primer extension assay (page 8503 fig 1 and 2). The cited art further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to **t**ctgagtca) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3).

However, Zhang does not teach a retroviral expression vector comprising a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site driving the expression of a growth hormone.

Miller teaches the making of a N2 and LNL6 based **retroviral vectors** comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang. One would have been motivated to do so because retroviral vectors has increased transfection efficiency as compared to plasmid base DNA transfection system. One would have reasonable expectation of success in doing so since making a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. In addition given the broadest reasonable interpretation to the method of expressing a transcript in a cell *(wherein the cell is an isolated cell in-vitro*) one would have reasonable expectation of success in infecting the cell in-vitro using the above described retroviral vector. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claims 37-40, 47-50, 54-57 and 60-63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record*) in view of Miller et al (Biotechniques 7(9):980-990, 1989 *ref of record*) as applied to claims 33-36, 41-46, 51-53 and 58-59 above, and further in view of Jarman et al (Mol. Cell. Bio. 11(9):4679-4689, 1991; *ref of record*), for the same reasons of record as set forth in the office action mailed on 05/27/04.

The instant claims are drawn to an expression vector comprising a transcriptional start site; a promoter operably linked to the transcriptional start site; and a ζ-globin enhancer (SEQ ID NO:1, 2 or 3) operably linked to the promoter, wherein the expression vector is a viral vector.

Zhang and Miller are discussed in detail above. Jarman teaches a major regulatory element upstream of the human ζ-globin gene cluster, which comprises nucleotide sequences that matches 99.9% and 99.6% to the nucleotide sequences of

SEQ ID NO: 2 and 3 of the instant application (page 4684, fig-5; and *the attached PTO sequence search report*). However, the nucleotide sequences as taught by Jarman does not contain a point mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca).

A retroviral vector wherein the gene of interest encodes a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone has been found obvious to one ordinary skill in the art at the time of filing in view of Zhang and Miller as stated above. It would have been further obvious to make a retroviral vector wherein the nucleotide sequences comprising the HS-40 enhancer region as taught by Zhang has been replaced by the nucleotide sequences as taught by Jarman. It would have been further obvious introduce a point mutation (gctgagtca to tctgagtca) in the HS-40 enhancer region (see Zhang, page 2304, fig-7) into the nucleotide sequences as taught by Jarman. One would have been motivated to do so because changing gctgagtca to tctgagtca enhances the transcription of a gene of interest (GH) operably linked the mutated HS-40 enhancer, therefore increasing the production of GH in genetically engineered cells (see Zhang page 2304, fig-7). One would have reasonable expectation of success in doing so, since making a point mutation and constructing a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. In addition the method of expressing a transcript in an isolated cell were within the reach of one ordinary skill in the art at time of filing and one would have reasonable expectation of success in infecting the cell in-vitro using the retroviral vector as describe above. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments

Regarding the prior art rejections above the applicant argues that the enhancer element may not function in a viral vector as suggested by McCune *(a reference cited by the applicant in support)*. Therefore Zhang and Miller would have not motivated one to make a viral vector containing an enhancer in the way suggested by the combined teaching of prior art. The applicant argues that McCune relates to general problem of sustaining expression of retrovirus-transduced genes in primary tissues, therefore one

skilled in the art would not expect that an enhancer including one containing SEQ ID NO:1 may function in a viral vector. The applicant argues that due to lack of a reasonable expectation of success, one skilled in the art would have not been motivated to include in the Miller vectors the HS40 enhancer taught in Zhang. The applicant concluded that invention as claimed is not obvious in view of cited art of record.

However, this is found NOT persuasive because the response element as taught by McCune is not limited to the response element as claimed i.e. SEQ ID NO:1, therefore there is reasonable expectation of success that a response element other than as taught by McCune would function in any viral (retroviral) vector as claimed. The office recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention.

Zhang teaches an expression vector comprising, a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). Zhang further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif, gctgagtca to **t**ctgagtca (SEQ ID NO:1, ζ-globin enhancer) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (see Zhang page 8502, col.2 para.6; page 8504 fig-3, page 2304, fig-7). Miller teaches the making of a N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3). Therefore it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific ζ-globin promoter

operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang and Jarman. In addition as one would have a reasonable expectation of success, since McCune does not specifically teach that the response element as claimed i.e. SEQ ID NO:1 would not work in a viral vector. In addition as discussed during the interview conducted on 05/27/04, various retroviral vectors encoding tissue specific enhancer elements were known in the art at the time of the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is

571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to ***(571) 272-0547.***

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306.**

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER